REMARKS

Prior to the present reply, claims 1-22 and 24-39 were pending. Due to a restriction requirement, claims 31-35 have been withdrawn from consideration. In the action dated June 18, 2010, claims 1-22, 24-29, and 36-39 are under examination. Claims 22, 28, and 29 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 1-22, 24-29, and 36-39 are rejected under 35 U.S.C. § 103(a) as being obvious over WO 01/04156 ("Larsen")[1] in view of Roach et al., Diabetes Care 22:1258-61, 1999 ("Roach"). Claims 1-22, 24-29, and 36-39 are also rejected for obviousness-type double patenting over claims 1-8 of U.S. Application No. 12/277,148. Claims 22 and 28 are further rejected under 35 U.S.C. § 112, first paragraph, for the introduction of new matter. Each of these rejections is addressed below.

Claim amendments

Claims 1, 2, 3, 6, 7, and 22 have been amended, and new claims 79-91 have been added. Claim 1 has been amended to incorporate the language of claim 2 as step (b) and to recite administration of the GLP-1 agonist following the drug holiday as step (c). Support for step (c) of claim 1 is found, for example, at page 6, lines 21-24. Claim 2 has been amended to require that the drug holiday be repeated at least one time. Support for this change is found, for example, at page 6, lines 24-25. Claim 3 has been amended to depend from claim 1. The language of claim 6 has been amended for consistency with language of amended claim 1. Claim 7 has been amended to require that the second endpoint is determined by an inability to control fasting blood glucose. Support for this amendment is found, for example, at page 12, lines 1-4.

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[1]The action cites PCT Publication WO **91**/04156, which the Office indicates was cited on applicant's IDS. WO **01**/04156 was cited on applicant's IDS and discloses the des Pro^{36}-exendin-4(1-39)-Lys_6-NH_2 mentioned in the action. Applicant therefore concludes the Office intended to cite WO 01/04156.

Claim 22 has been amended to recite that the GLP-1 agonist is exendin-4 or an exendin-4 analog comprising an amino acid sequence at least 90% identical to exendin-4. Support for a GLP-1 analog having 90% identity to exendin-4 is found, for example, at page 16, line 27.

New claim 79 recites that the GLP-1 agonist is COMPOUND 1. Support for this claim is found, for example, in original claim 21. New claims 80, 88, and 89 recites that the diabetes is type II diabetes. Support for these claims is found, for example, at page 21, lines 14-16 and at page 22, lines 17-20. New claim 81 recites that the GLP-1 agonist is exendin-4. Support for this claim is found, for example, in original claim 22. New claim 82 recites that steps (b) and (c) of claim 1 are repeated at least twice. Support for this change is found, for example, at page 6, lines 24-25. New claims 83 and 84 depend from claim 7 and recite that the increase in fasting blood glucose is at least 5% and at least 10%, respectively. Support for these claims is found, for example, at page 12, lines 1-4. New claim 85 recites that the second endpoint is characterized by an increase in glycosylated hemoglobin, and new claims 86 and 87 recite that increase is at least 5% and at least 10%, respectively. Support for these claims is found, for example, at page 12, lines 4-6. New claim 90 recites that the GLP-1 agonist is exendin-4. Support for this claim is found, for example, in original claim 22. New claim 91 recites that the GLP-1 agonist is $Arg^{34}Lys^{26}$-(*N*-ε-(γ-Glu(*N*-α-hexadecanoyl)))-GLP-1[7-37]. Support for this claim is found in original claim 21. In particular, the subject matter of claim 91 is found in U.S. Patent No. 6,268,343 (the '343 patent) at column 267, lines 53-54. Because the '343 patent is properly incorporated by reference under 37 C.F.R. §§ 1.57(b) and (c) as set forth at page 11, lines 17-21, and at page 43, line 13, this material can support new claim 91. These amendments add no new matter.

Information disclosure statement

Applicant respectfully resubmits the materials that were crossed out on the Information Disclosure Statement that was filed March 18, 2010. On the returned Form PTO-1449, the Office indicates that these materials were not considered because there is no listing of authors or publication dates. These materials were provided from the prosecution of corresponding International and European patent applications. Applicants respectfully note that 37 C.F.R. § 1.98(b) provides specific instructions for citing four categories of documents: U.S. Patents, U.S. Patent Applications, foreign patents, and publications. There is however, this rule does not provide instructions relating to citation of any other materials, including those from corresponding foreign patent applications, such as those being submitted herewith. Accordingly, Applicant believes this information has been properly identified and that it is improper for the Office to refuse consideration of this information.

Nonetheless, Applicant, to the extent possible, has provided information such as authors and dates with the material in question on the Form PTO-1449 submitted concurrently with this reply. Consideration of this information is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

Claims 22, 28, and 29 are rejected as failing to comply with the written description requirement. In making this rejection, the Office asserts that the application fails to show possession of the recited exendin-4 derivatives of claim 22 or the insulin analogs of claims 28 and 29. Each of these rejections is addressed below.

Claim 22

In rejecting claim 22, the Office states that the claim includes exendin-4 fragments of any length and that no such fragments with the required functional property are

disclosed. Without assenting to this rejection, claim 22 has been amended to delete reference to exendin-4 fragments. Following this amendment, claim 22 recites an analog or derivative that comprises an amino acid sequence at least 90% identical to exendin-4. Because the specification discloses numerous examples of such analogs (see, e.g., the exendin-4 analogs of claim 21), the application demonstrates that Applicant had possession of the analogs recited in amended claim 22. Withdrawal of this rejection is respectfully requested.

Claims 28 and 29

Claims 28 and 29 are rejected on the grounds that the specification fails to adequately describe insulin analogs that are recognized as antidiabetic drugs. Applicant respectfully traverses.

In their previous response, Applicant provided the results of search from the FDA website. These results provide two important pieces of information. First, these results demonstrate that the number of insulin analogs recognized as antidiabetic drugs are limited in number. The search also provides evidence that such analogs can be readily identified.

In the present action, the Office dismisses this evidence because the search is recent and therefore cannot demonstrate what would have been known in the art at the time of filing the present application. Further, the Office takes the position that the statement "products listed on this page may not be equivalents of one another," which is found on the search page, renders it unclear as to what the products on the search page actually represent.

To reject a claim for as failing to comply with the written description requirement, the Office must:

> Establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that

> the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.

MPEP § 2163.04(I)(B). In the present action, the Office has failed to provide any such reasons. Indeed, the Office only taken issue with alleged deficiencies of Applicant's evidence. Because the Office has not presented a *prima facie* case to support a finding of a lack of written description for the claimed genus of insulin analogs, withdrawal of this rejection is respectfully requested.

Indeed, the genus in question (insulin analogs that are recognized as antidiabetic agents) would have been have been in the possession of one skilled in the art at the time the application was filed. The skilled artisan, i.e., a trained scientist or physician, would likely know the identity of insulin analogs that are recognized as antidiabetic drugs. This is set forth in the accompanying Declaration of Keld Fosgerau, Ph.D. under 37 C.F.R. § 1.132 ("the Declaration"). As explained in the Declaration, a skilled scientist working the field of the invention at the filing date of the present application either would have knowledge of insulin analogs that are recognized as antidiabetic drugs or would have readily been able to ascertain the identity of such analogs. The Declaration further points to a review article that discusses therapeutic insulin analogs.

The search results provided by Applicant with the previous reply simply demonstrate that it would be easy for the skilled artisan to identify members of the claimed genus of insulin analogs. Thus, even if the skilled artisan were not aware of every member of the claimed genus, this artisan could use, for example, a standard reference text, a review article in a scientific journal, or the FDA website to identify such analogs.

For all of these reasons, claims 28 and 29 satisfy the written description requirement. Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1-22, 24-29 and 36-39 are rejected as being obvious over Larsen in view of Roach. In making this rejection, the Office cites Larsen as teaching administration of des Pro^{36}-exendin-4(1-39)-Lys_6-NH_2 for the treatment of diabetes and Roach as teaching administration of Lispro for the treatment of diabetes. Based on these combined teachings and on the assertion that the claimed dosing regimen is "routine optimization," the Office concludes that the claimed methods would have been obvious to one skilled in the art. Specifically, the Office states that, in diabetes, blood glucose levels are routinely monitored and that administration of antidiabetic is administered as needed based on glucose levels. The Office therefore asserts that the drug would have been taken as needed, and thus concludes that the claims are obvious. Applicant respectfully traverses.

There is no suggestion to reduce or cease administration of a GLP-1 agonist

To establish a case of *prima facie* obviousness, the Office must provide some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. MPEP § 2142. As an initial matter, claim 1 has been amended to require a dosing regimen that includes a "drug holiday," in which the administration of the drug is reduced below the therapeutically effective level (e.g., ceased) for a time, followed by a resumption of administration at an effective level. As explained below, the Office has provided no evidence to support the contention that dosing a GLP-1 agonist in this manner would be obvious.

The Office is incorrect in asserting that a diabetic subject would monitor blood glucose and, based on this monitor, would administer a GLP-1 agonist on an as-needed basis. While this may be the case for insulin or insulin analogs, this is not the case for GLP-1 agonists. Indeed, the GLP-1 agonists currently being marketed for diabetes treatment, Byetta (exenatide; synthetic exendin-4) and Victoza (liraglutide; modified GLP-1), are administered on an invariant dosing schedule: either once or twice daily at a

particular dosage. Byetta is indicated for twice daily subcutaneous administration (see Byetta label, attached as Exhibit A) no more than sixty minutes prior to morning and evening meals. While the label indicates that the dose should be increased from 5 μg to 10 μg after one month, the label states that the reason for starting at 5 μg is to reduce intensity and severity of gastrointestinal side effects.

Victoza is similarly indicated for once-a-day administration (see Victoza label, attached as Exhibit B). While the label suggests increasing the dosage depending the glycemic effect, there is no suggestion that one should routinely monitor blood glucose levels to determine whether administration should be *reduced* below the therapeutically effective level or eliminated for a period of time. Indeed, the label suggests only *increasing* the dosage, if the desired effect is not achieved at a lower dose.

Thus, neither Byetta nor Victoza are indicated for a dosing regimen in which administration is ever reduced below the therapeutically effective amount or is eliminated for a time before resuming a therapeutically effective dosage. Accordingly, the currently marketed GLP-1 agonists do not use or suggest the dosing approach required by claim 1.

GLP-1 agonists under development likewise take an approach entirely divergent from that of the present application. Bydureon, an extended-release form of Byetta formulated for one-weekly administration, is currently undergoing clinical trials. This formulation is designed to maintain a *continuous presence* of the active ingredient (see page 1488, first column, first full paragraph of Kim et al., Diabetes Care 30:1487-93, 2007, attached as Exhibit C), which is in sharp contrast to the "drug holiday" approach presently claimed.

Given that others in the field are using an approach very different from the one claimed, and because the Office has provided no evidence to suggest administration of a GLP-1 agonist in diabetes using the claimed "drug holiday" dosing regimen, the Office has failed to set forth a *prima facie* case of obviousness. For these reasons, withdrawal of the § 103(a) rejection is respectfully requested.

Neither Larsen nor Roach disclose the benefit of "drug holiday" approach

An unexpected result can form the basis for a finding of non-obvious. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), in its comments on *United States v. Adams* (383 U.S. 39 (1966)), supports a finding of nonobviousness in view of an unexpected result:

> The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was *not obvious* to those skilled in the art. (Emphasis added).

KSR at 416. At page 3 of the action, the Office has acknowledged that Applicant's discovery of the therapeutic benefits of GLP-1 agonist administration continuing for a significant period of time period after administration of the agonist ends is unexpected. The Office, however, takes the position that this property has only been shown for des Pro^{36}-exendin-4(1-39)-Lys_6-NH_2 ("COMPOUND 1") and that these results cannot be generalized to all GLP-1 agonists.

In response, Applicant now provides evidence indicating that these results can in fact be generalized to all GLP-1 agonists. The Declaration provides experimental evidence indicating that two GLP-1 agonists, Byetta (exenatide) and Victoza (liraglutide), exhibit similar properties to COMPOUND 1. As with COMPOUND 1, administration of either Byetta or Victoza for 50 days, followed cessation of administration for at least 40 days, resulted in decreased blood glucose levels in diabetic mice during this latter period, as compared to controls receiving a vehicle for the duration of the experiment. Based on these data, one skilled in the art would appreciate that the identity of the GLP-1 agonist is not critical to the observed therapeutic benefit following cessation of administration. Thus, the results presented in the application are applicable to GLP-1 agonists in general.

Because the benefits associated with the claimed dosing regimen can be generalized across the scope of the claimed GLP-1 agonists, these findings support a

conclusion of non-obviousness. For this reason as well, withdrawal of the § 103(a) rejection is respectfully requested.

Obviousness-type double patenting rejection

Applicant requests that this rejection be held in abeyance. Once the other rejections have been addressed, it would be proper to allow the present claims to issue as the present application is the earlier filed of the two applications (M.P.E.P. § 804(I)(B)(1)).

New rejection under 35 U.S.C. § 112, first paragraph (new matter)

Claims 22 and 28 are rejected as containing new matter. Each of these rejections is addressed below.

Claim 22

Claim 22 is rejected on the grounds that the specification does not provide support for 90% identical *fragments* of exendin-4 or any homologs of exendin-3. Further, the Office contends that there is no support for the function limitation "increases endogenous insulin production."

Claim 22 has been amended to delete reference to exendin-4 fragments and exendin-3, and to delete the language regarding "increases in endogenous insulin production. Based on these amendments, the Office's rejection of this claim has been rendered moot.

As amended, claim 22 recites exendin-4 and exendin-4 analogs or derivatives that include an amino acid sequence 90% identical to exendin-4. Written support for exendin-4 is found, for example, in claim 22 as filed. As explained above, support for the recited exendin-4 analogs or derivatives is found, at page 16, line 27. Accordingly, amended

claim 22 does not introduce new matter. Withdrawal of this rejection is respectfully requested.

Claim 28

Claim 28 recites an insulin analog that is a recognized antidiabetic drug. The Office contends that this language is not supported by the specification. Applicant respectfully disagrees.

Applicant directs the Office's attention to page 20 lines 18-20 (emphasis added):

> Practice of the invention methods described herein is fully compatible with the use of one or a combination of *recognized antidiabetic drugs* including what is often referred to as a "cocktail" approach.

Applicant further points to page 20, lines 25-26 (emphasis added):

> For instance, and in one embodiment of the method, *at least one of the antidiabetic drugs is* insulin, *an insulin analog*; or a pharmaceutically acceptable mixture thereof.

These passages indicate that the method of the invention may include use of a recognized antidiabetic drug and that the antidiabetic drug may be an insulin analog. Taken together, one skilled in the art would appreciate that the specification supports the use of an recognized antidiabetic drug that is an insulin analog and thus provides support for claim 28. Withdrawal of this rejection is accordingly requested.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the final Office action for three (3) months, to and including December 20, 2010, as December 18, 2010 falls on a Saturday. Also enclosed is a Request for Continued Examination.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Dec 24, 2010

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